Zenith Goldline
PHARMACEUTICALS

May 24, 1999

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Citizen Petition Relating to Standards and Procedures for Patient Registries for Clozapine

Dear Sir or Madam:

Zenith Goldline Pharmaceuticals submits this petition under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDC Act), and 21 C.F.R. §§ 10.25 and 10.30 of the regulations, to request that the Commissioner of Food and Drugs refrain from approving abbreviated new drug applications (ANDAs) for clozapine until the Food and Drug Administration (FDA) develops standards and procedures for patient registries. As determined by FDA, patient registries are necessary to assure the safe use of clozapine. Without FDA standards and procedures governing patient registries, patients treated with clozapine may be placed at increased risk of agranulocytosis, a potentially lethal condition. Informal arrangements among marketers of clozapine products, developed after approval has been granted, cannot continue to be relied on to provide the patient protection required as a condition of making clozapine safely available to treat patients. With the approval of multiple generic clozapine ANDAs, the failure to establish formal guidelines for clozapine patient registries may significantly impact patient safety because

the proliferation of patient registries will confuse health care providers due to the variation in operating system, levels of internal control and safeguards.

Action Requested

This petition requests that FDA institute a public proceeding to formally develop minimum standards and procedures for clozapine patient registries. The petition also requests that FDA refrain from approving any ANDAs for clozapine until such standards and procedures have been proposed in the Federal Register.

A. Statement of Grounds

1. Clozapine indication and side effects

First approved for use in the United States in 1989, clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment. As described in the Zenith Goldline package insert attached as Appendix A, clozapine has serious side effects, including the significant risk of agranulocytosis[1] and seizure. Therefore, clozapine is only indicated for use in patients for whom appropriate courses of standard antipsychotic drugs have either been ineffective or have caused intolerable side effects. Although not a common adverse reaction (1.3% in clinical trials), agranulocytosis can be fatal. There are no established risk factors for clozapine-induced agranulocytosis. Accordingly, monitoring for the

[1] Agranulocytosis is a potentially life threatening condition defined in the Zenith Goldline package insert as an absolute neutrophil count (ANC) of less than $500/mm^3$.

effects of bone marrow suppression — reduced white blood cell (WBC) counts — is the only means for early detection of this adverse reaction.

2. Clozapine labeling and patient registry

The labeling for clozapine contains emphatic warnings about the risk of clozapine-induced agranulocytosis and a detailed protocol for monitoring WBC counts to detect its possible onset. Monitoring intervals range from daily to biweekly, depending on the results of WBC testing. If the WBC count falls below a threshold of $3500/mm^3$, or drops by a substantial amount from baseline, clozapine treatment may continue but with increased monitoring. If the WBC count falls below $3000/mm^3$, clozapine treatment is interrupted, daily WBC monitoring is instituted, and treatment is resumed only if the WBC count returns to $3500/mm^3$. If the WBC count falls below $2000/mm^3$, clozapine treatment is terminated, and may not be resumed. Required WBC monitoring continues for four weeks after discontinuation of clozapine therapy for any reason.

The risks associated with developing fatal agranulocytosis can be decreased when the product is prescribed in accordance with the package insert and patients are monitored through a patient registry. Novartis, the sponsor of the NDA for Clozaril brand of clozapine, in consultation with FDA, developed a patient registry system to reinforce the product labeling. As currently constituted, the system provides for:

- Availability of clozapine only through audited physicians and pharmacists.

- Agreement by enrollees to adhere to the WBC monitoring protocol.
- Dispensing of clozapine only if WBC test results are presented to the pharmacist and only if the patient is not listed in the non-rechallenge masterfile.
- Submission of WBC test results and clozapine dispensing information to the patient registry.
- Maintenance of a non-rechallenge masterfile.

In addition to these essentially mandatory elements of the patient registry system, both current registries also audit the information submitted for each patient to confirm that prescription and dispensing of clozapine accord with the labeled protocol. If a discrepancy is identified, a registry employee contacts the physician and pharmacist to resolve it. Thus, although the health care providers are primarily responsible for assuring that the results of WBC monitoring are translated into appropriate drug treatment decisions, this auditing function carried out by a clozapine patient registry enhances the health care providers' ability to manage their patients.

3. Coordination of patient registries

Zenith Goldline's ANDA for clozapine was approved in November 1997. Prior to the approval, Zenith Goldline worked closely with FDA to develop a clozapine patient registry that would provide the same safety features as the Novartis registry. Zenith Goldline recognized the need for interactions between its patient registry and that

maintained by Novartis and requested that FDA facilitate communications on this issue. Novartis, which was initially uncooperative with Zenith and FDA, sought to delay addressing the issue of coordinated patient registries. However, subsequent to the approval of Zenith's clozapine, FDA ordered a joint meeting with representatives of Zenith Goldline and Novartis to coordinate the standards and procedures for the two companies' clozapine patient registries. This joint meeting addressed a number of issues as set out below.

a. Non-rechallenge masterfile. The non-rechallenge masterfile is a confidential file which contains the identities of all patients who developed clozapine induced WBC counts below 2000/mm^3. These patients are at high risk of agranulocytosis from clozapine, especially upon resumption of clozapine exposure after discontinuation. Accordingly, clozapine may not be dispensed to a patient listed in the non-rechallenge masterfile. Compliance with this prohibition is assured by the requirement that the health care provider must obtain an eligibility code from the patient registry for any patient new to the provider.

At the joint meeting with FDA, it was decided that Novartis would maintain the non-rechallenge masterfile. Zenith Goldline would query the masterfile as part of issuing an eligibility code for a patient for whom Zenith Goldline clozapine was prescribed. Zenith Goldline would also provide, for inclusion in the masterfile, the identities of patients who acquired non-rechallenge status while being treated with Zenith Goldline clozapine.

b. At-risk patients. A second function of the patient registry system that warranted specific attention was the ability of the system to help safeguard at-risk patients, i.e., patients with declining or marginal blood counts. This function of the patient registry depends on the ability of the patient registries to provide information on patients in order to enhance the decision making ability of the clinician. The health care provider (physician or pharmacist) may seek information from the patient registries in order to obtain a patient's full clozapine history. Subsequently, the health care provider would reconcile the data from the patient registries for review.

Complete information can be critical if the patient's WBC count is being closely tracked due to the clozapine protocol requirements. Although the health care providers to the patient have primary responsibility for determining a patient's relevant treatment history from customary sources, the clozapine patient registries provide a valuable safeguard. Not only do the patient registries serve as a repository of WBC data on a patient, they also permit registry employees to audit the results of monitoring and to communicate advisory information to health care providers.

Failure of individual company patient registries to provide information, reliably and expeditiously, would undermine the patient registry system's safeguard function. Worse, it could increase the risk to patients because health care providers rely on the patient registry information in preference to using other sources of patient treatment history.

At the joint meeting, FDA concluded that the companies would manage this function of the patient registries without specific guidance from the agency. Informally, the companies agreed that the reciprocal exchange of information regarding the three most recent WBC counts for all registered patients would support the safeguard function of the patient registries and minimize the risk of inadvertent deviation from the clozapine dosing protocol.

4. **Experience with Zenith Goldline/Novartis arrangement**. Zenith Goldline and Novartis have successfully operated the two patient registries to achieve the objectives of the clozapine patient registration system — adherence to the clozapine labeling protocol, avoidance of inappropriate clozapine administration, and, generally, safe use of clozapine as an important treatment for seriously ill patients who could not be adequately treated without it.

5. **Need for explicit standards and procedures**. The success of the coordinated patient registry system has been due in part to the fact that only two companies currently market clozapine. The addition of other patient registries has the potential to jeopardize patient safety unless FDA develops explicit requirements for all companies that sell clozapine. The likely result of continued reliance on informal arrangements, developed ad hoc after the approval of each ANDA, will be a progressive erosion in the reliability of the clozapine patient registry system.

The current informal arrangement works for several reasons. First, health care providers know that, at this time, only Novartis and Zenith Goldline sell clozapine and operate patient registries. It is not difficult to avoid making paperwork mistakes when only two systems are operating. It will become more difficult to avoid such mistakes as the systems proliferate, with more forms, more phone numbers, and more addresses added to information providers must keep track of.

Second, the current arrangement works because the registries themselves can correct provider mistakes. Now, if Zenith Goldline receives information about a patient not in its patient registry, the registry employee can forward it to the Novartis patient registry, and vice versa. With more registries, the ability to nullify paperwork errors in this simple way will be degraded with each new entrant, to the point where it will disappear altogether. Zenith Goldline has documented several tracking errors by health care providers where information that should have been provided to Novartis was in fact given to Zenith Goldline. This confusion reduced the time Novartis had to react to the situation. As the number of patient registries increases, these incidents will increase because physicians, pharmacists and even the patient registries may be confused over which clozapine patient registry holds a particular patient's information. This inability to reconcile paperwork errors will lead to a lack of meaningful WBC count monitoring and therefore increase patient risk.

A failure by the clozapine patient registry system as a whole thus becomes more likely as it becomes fragmented among more and more individual clozapine

manufacturers. It is obviously not possible for Zenith Goldline to demonstrate, with empirical data, that this process will have concrete adverse results at any particular time, or with the approval of one additional clozapine ANDA, as opposed to two or three. Nor is there a necessity to make that kind of showing. It is self-evident that the potential for systems errors increases with the number of organizational units that are required to communicate and coordinate with each other, and the number of different parallel communications systems available for customers to use.

The consequences of a breakdown in the clozapine patient registry system may be manifested in a variety of ways. A worst case scenario is a rechallenge with clozapine of patients who should not receive the drug. This could occur due to failed reporting to the non-rechallenge master file or, even more likely, through failure to identify a declining WBC count due to either inadequate WBC monitoring or fragmented patient histories spread across three or more patient registries. These consequences are serious, but they can be avoided through the issuance of clozapine patient registry guidelines by FDA.

Informal arrangements can be reached among Zenith Goldline and Novartis, on the one hand, and subsequent entrants on the other, as was done when Zenith Goldline obtained approval to market clozapine. But neither FDA nor Zenith Goldline can predict whether those arrangements will work in practice. Informal arrangements among drug sponsors are subject to inconsistent interpretations, different levels of organizational commitment, and other forms of unreliability. These informal arrangements are not an appropriate means of addressing issues of drug risk in a situation where the agency has

determined that the patient risk is sufficiently grave to require a patient registry to reduce the risk. If informal arrangements were adequate in such circumstances, many FDA regulations and guidelines could be dispensed with. Regulations and guidelines are necessary to establish explicit, uniform FDA standards that regulated entities can identify, and be held to by the agency. Such standards should be in place for clozapine patient registries prior to the approval of any additional ANDAs for clozapine.

6. **Legal authority**. The agency has the inherent authority under the Administrative Procedure Act to issue guidelines governing the clozapine patient registries. Under the FDC Act, it has the authority to issue regulations necessary for the efficient enforcement of the statute. 21 U.S.C. § 371(a). Therefore, FDA has a legal basis for issuing either guidelines or regulations establishing standards and procedures for clozapine patient registries required by approvals under 21 U.S.C. § 355. Zenith Goldline believes that such standards and procedures should be in the form of guidelines, rather than regulations. The guidelines should be developed in accordance with FDA's good guidance practices.

FDA has authority not to approve ANDAs for clozapine until such guidelines are in place. Under the FDC Act, an ANDA for clozapine must contain labeling that states that "clozapine is available only through a distribution system that ensures monitoring of WBC counts according to the schedule described below . . ." 21 U.S.C.§ 355(j)(2)(A)(v). In addition, the ANDA must contain information showing that the conditions of use for the proposed ANDA drug have previously been approved. 21 U.S.C. § 355(j)(2)(A)(i).

Without resolution of the issues raised by Zenith Goldline, the labeling for a third or subsequent clozapine product could not accurately represent that clozapine is available through a distribution system that "ensures" WBC monitoring in accordance with the labeling protocol. The addition of a third or subsequent clozapine product would threaten to undermine the patient registry system, which is an integral part of the distribution system, to a sufficiently serious extent that the word "ensures" would no longer be an accurate description. Moreover, whereas the conditions of use of Novartis's clozapine product as approved in the NDA were applicable to the Zenith Goldline ANDA for clozapine, the conditions proposed for a third or subsequent clozapine ANDA will, for the reasons explained, be fundamentally different as a result of those approvals. Consequently, the conditions of use for a proposed third or subsequent clozapine ANDA will not have been previously approved in the Novartis NDA for Clozaril.

B. Environmental Impact

A claim for categorical exclusion of the requirements for Environmental Assessment is made pursuant to 21 C.F.R. § 25.31(a) and (i).

C. Economic Impact

Provided on request.

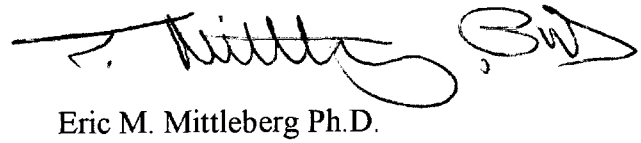
D. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies,

and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

Zenith Goldline Pharmaceuticals, Inc.



Eric M. Mittleberg Ph.D.
Vice President-Scientific Affairs

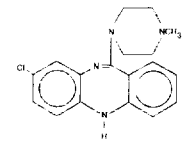
APPENDIX A

Clozapine Package Insert

CLOZAPINE TABLETS
Rx only

DESCRIPTION

Clozapine, an atypical antipsychotic drug, is a tricyclic dibenzodiazepine derivative. The chemical name of clozapine is 8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo [*b*,*e*][1,4] diazepine and it has the following structural formula:



$C_{18}H_{19}ClN_4$ MW 326.83

Clozapine is a yellow, crystalline powder, very slightly soluble in water. Each tablet, for oral administration, contains 25 mg or 100 mg clozapine. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, povidone, pregelatinized starch and talc.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clozapine is classified as an 'atypical' antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine-mediated behaviors differ from those exhibited by more typical antipsychotic drug products. In particular, although clozapine does interfere with the binding of dopamine at D_1, D_2 and D_5 receptors, and has a high affinity for the D_4 receptor, it does not induce catalepsy nor inhibit apomorphine-induced stereotypy. This evidence, consistent with the view that clozapine is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of clozapine from extrapyramidal side effects.

Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors.

Absorption, Distribution, Metabolism and Excretion

In man, clozapine tablets (25 mg and 100 mg) are equally bioavailable relative to a clozapine solution. Following a dosage of 100 mg b.i.d., the average steady state peak plasma concentration was 319 ng/mL (range: 102-771 ng/mL), occurring at the average of 2.5 hours (range: 1-6 hours) after dosing. The average minimum concentration at steady state was 122 ng/mL (range: 41-343 ng/mL), after 100 mg b.i.d. dosing. Food does not appear to affect the systemic bioavailability of clozapine. Thus, clozapine may be administered with or without food.

Clozapine is approximately 97% bound to serum proteins. The interaction between clozapine and other highly protein-bound drugs has not been fully evaluated but may be important. (See **PRECAUTIONS**)

Clozapine is almost completely metabolized prior to excretion and only trace amounts of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The demethylated, hydroxylated and N-oxide derivatives are components in both urine and feces. Pharmacological testing has shown the desmethyl metabolite to have only limited activity, while the hydroxylated and N-oxide derivatives were inactive.

The mean elimination half-life of clozapine after a single 75 mg dose was 8 hours (range: 4-12 hours), compared to a mean elimination half-life, after achieving steady state with 100 mg b.i.d. dosing, of 12 hours (range: 4-66 hours). A comparison of single-dose and multiple-dose administration of clozapine showed that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration dependent pharmacokinetics. However, at steady state, linearity dose-proportional changes with respect to AUC (area under the curve), peak and minimum clozapine plasma concentrations were observed after administration of 37.5 mg, 75 mg, and 150 mg b.i.d.

Human Pharmacology

In contrast to more typical antipsychotic drugs, clozapine therapy produces little or no prolactin elevation.

As is true of more typical antipsychotic drugs, clinical EEG studies have shown that clozapine increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs, and sharp wave activity and spike and wave complexes may also develop. Patients, on rare occasions, may report an intensification of dream activity during clozapine therapy. REM sleep was found to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.

INDICATIONS AND USAGE

Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment. Because of the significant risk of agranulocytosis and seizure associated with its use, clozapine should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs (see **WARNINGS**).

The effectiveness of clozapine in a treatment resistant schizophrenic population was demonstrated in a 6-week study comparing clozapine and chlorpromazine. Patients meeting DSM-III criteria for schizophrenia and having a mean BPRS total score of 61 were demonstrated to be treatment-resistant by history and by open, prospective treatment with haloperidol before entering into the double-blind phase of the study. The superiority of clozapine to chlorpromazine was documented in statistical analyses employing both categorical and continuous measures of treatment effect.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated.

CONTRAINDICATIONS

Clozapine is contraindicated in patients with a previous hypersensitivity to clozapine or any other component of this drug, in patients with myeloproliferative disorders, uncontrolled epilepsy, or a history of clozapine induced agranulocytosis or severe granulocytopenia. As with more typical antipsychotic drugs, clozapine is contraindicated in severe central nervous system depression or comatose states from any cause.

Clozapine should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The mechanism of clozapine induced agranulocytosis is unknown; nonetheless, it is possible that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression.

WARNINGS

General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (*SEE FOLLOWING*), CLOZAPINE SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZAPINE, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST 2 TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE, AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZAPINE MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THEREAFTER FOR THE FIRST SIX MONTHS. IF ACCEPTABLE WBC COUNTS (WBC greater than or equal to 3,000/mm³ with an ANC greater than or equal to 1,500/mm³) HAVE BEEN MAINTAINED DURING THE FIRST 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNTS CAN BE MONITORED EVERY OTHER WEEK. WBC COUNTS MUST BE MONITORED WEEKLY FOR AT LEAST 4 WEEKS AFTER THE DISCONTINUATION OF CLOZAPINE.

CLOZAPINE IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WBC COUNTS ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION.

Agranulocytosis

Agranulocytosis, defined as an absolute neutrophil count (ANC) of less than 500/mm³, has been estimated to occur in association with clozapine use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 US cases out of 1743 patients exposed to clozapine during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported worldwide in association with clozapine use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of clozapine-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for clozapine-induced agranulocytosis, despite strict adherence to the required frequency of monitoring. In the US, under a weekly WBC monitoring system with clozapine, there have been 585 cases of agranulocytosis as of August 21, 1997; 19 were fatal. During this period 150,409 patients received clozapine. A hematologic risk analysis was conducted based upon the available information in the Clozaril™ National Registry (CNR) for US patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule, rose steeply during the first two months of therapy, peaking in the fourth month. Among clozapine patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree, so that by the sixth month the weekly incidence of agranulocytosis was reduced to 3 per 1000 person-years. After six months, the weekly incidence of agranulocytosis declines still further, however, never reaches zero. It should be noted that any type of reduction in the frequency of monitoring WBC counts may result in an increase incidence of agranulocytosis.

Because of the substantial risk for developing agranulocytosis in association with clozapine use, which may persist over an extended period of time, patients must have a blood sample drawn for a WBC count before initiation of treatment with clozapine, and must have subsequent WBC counts done at least weekly for the first six months of continuous treatment. If WBC counts remain acceptable (WBC greater than or equal to 3000/mm³, ANC >1500/mm³) during this period, WBC counts may be monitored every other week thereafter. After the discontinuation of clozapine, weekly WBC counts should be continued for an additional 4 weeks.

If a patient is on clozapine therapy for less than 6 months with no abnormal blood events and there is a break on therapy which is less than or equal to 1 month, then patients can continue where they left off with weekly WBC testing for 6 months. When this 6 month period has been completed, the frequency of WBC count monitoring can be reduced to every other week. If a patient is on clozapine therapy for less than 6 months with no abnormal blood events and there is a break on therapy which is greater than 1 month, then patients should be treated weekly for an additional six-month period before biweekly testing is initiated. If a patient is on clozapine therapy for less than 6 months and experiences an abnormal blood event as described below but remains a rechallengeable patient (patients cannot be reinitiated on clozapine therapy if WBC counts fall below 2000/mm³ or the ANC falls below 1000/mm³ during clozapine therapy), the patient must restart the six-month period of weekly WBC monitoring at day 0.

If a patient is on clozapine therapy for 6 months or longer with no abnormal blood events and there is a break on therapy which is 1 year or less, then the patient can continue WBC count monitoring every other week if clozapine therapy is reinitiated. If a patient is on clozapine therapy for 6 months or longer with no abnormal blood events and there is a break on therapy which is greater than 1 year, then, if clozapine therapy is reinitiated, the patient must have WBC counts monitored weekly for an additional 6 months. If a patient is on clozapine therapy for 6 months or longer and subsequently has an abnormal blood event, but remains a rechallengeable patient, then the patient must restart weekly WBC count monitoring until an additional 6 months of clozapine therapy has been received. The distribution of clozapine is contingent upon performance of the required blood tests.

Treatment should not be initiated if the WBC count is less than 3500/mm³, or if the patient has a history of a myeloproliferative disorder, or previous clozapine-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection.

If, after the initiation of treatment, the total WBC count has dropped below 3500/mm³ or it has dropped by a substantial amount from baseline, even if the count is above 3500/mm³, or if immature forms are present, a repeat WBC count and a differential count should be done. A substantial drop is defined as a single drop of 3,000 or more in the WBC count or a cumulative drop of 3,000 or more within 3 weeks. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500/mm³ and an ANC above 1500/mm³, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000/mm³ or the ANC below 1500/mm³, clozapine therapy should be interrupted, WBC count and differential should be performed daily, and patients should be carefully monitored for flu like symptoms or other symptoms suggestive of infection. Clozapine therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000/mm³ and the ANC returns to levels above 1500/mm³. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500/mm³.

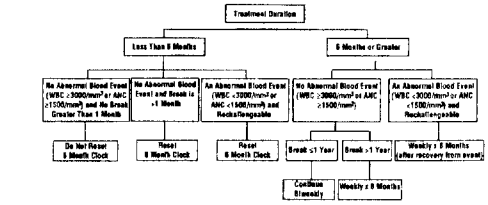
If the total WBC count falls below 2000/mm³ or the ANC falls below 1000/mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000/mm³, or ANCs below 1000/mm³ during clozapine therapy should have daily WBC count and differential. These patients should not be re-challenged with clozapine. Patients discontinued from clozapine therapy due to significant WBC suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during clozapine therapy, a single, national master file will be maintained confidentially.

Except for evidence of significant bone marrow suppression during initial clozapine therapy, there are no established risk factors, based on world-wide experience, for the development of agranulocytosis in association with clozapine use. However, a disproportionate number of the US cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during domestic development of clozapine. Most of the US cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with clozapine use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with clozapine.

To reduce the risk of agranulocytosis developing undetected, clozapine is available only through a distribution system that ensures monitoring of WBC counts according to the schedule described above prior to delivery of the next supply of medication.

Interrupted Therapy (WBC<3000/mm³ ANC<1500/mm³) for Bi-Weekly Monitoring



Eosinophilia

In clinical trials, 1% of patients developed eosinophilia, which, in rare cases, can be substantial. If a differential count reveals a total eosinophil count above 4,000/mm³, clozapine therapy should be interrupted until the eosinophil count falls below 3,000/mm³.

Seizures

Seizure has been estimated to occur in association with clozapine use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to clozapine during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher clozapine doses used.

Caution should be used in administering clozapine to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Adverse Cardiovascular and Respiratory Effects

Orthostatic hypotension with or without syncope can occur with clozapine treatment and may represent a continuing risk in some patients. Rarely (approximately 1 case per 3,000 patients), collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in associations with rapid dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. When restarting patients who have had even a brief interval off clozapine, i.e., 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25 mg tablet (12.5 mg) once or twice daily (see DOSAGE AND ADMINISTRATION).

Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking clozapine, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.

A minority of clozapine treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of clozapine. The clinical significance of these changes is unclear. However, in clinical trials with clozapine, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, arrhythmias and sudden death. In addition there have been postmarketing reports of congestive heart failure, myocarditis, with or without eosinophilia, and pericarditis/pericardial effusions in association with clozapine use. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown.

Clozapine should be used with caution in patients with known cardiovascular and/or pulmonary disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

There have been several reported cases of NMS in patients receiving clozapine alone or in combination with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that clozapine may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. A few cases of tardive dyskinesia have been reported in patients on clozapine who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to clozapine alone. Nevertheless, it cannot be concluded, without more extended experience, that clozapine is incapable of inducing this syndrome.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptom suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, clozapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic clozapine use should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on clozapine, drug discontinuation should be considered. However, some patients may require treatment with clozapine despite the presence of the syndrome.

PRECAUTIONS

General

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. Although it is not known whether the risk would be increased, it is prudent either to avoid clozapine or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.

Fever

During clozapine therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first 3 weeks of treatment. While this fever is generally benign and self limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of Neuroleptic Malignant Syndrome (NMS) must be considered. There have been several reports of NMS in patients receiving clozapine, usually in combination with lithium or other CNS-active drugs. (See **Neuroleptic Malignant Syndrome (NMS)**, under **WARNINGS**.)

Pulmonary Embolism

The possibility of pulmonary embolism should be considered in patients receiving clozapine who present with deep vein thrombosis, acute dyspnea, chest pain or with other respiratory signs and symptoms. As of December 31, 1993 there were 18 cases of fatal pulmonary embolism in association with clozapine therapy in users 16-54 years of age. Based upon the extent of use observed in the Clozaril National Registry, the mortality rate associated with pulmonary embolus was 1 death per 3450 person-years of use. This rate was about 27.5 times higher than that in the general population of a similar age and gender (95% Confidence Interval: 17.1, 42.2). Deep vein thrombosis has also been observed in association with clozapine therapy. Whether pulmonary embolus can be attributed to clozapine or some characteristic(s) of its users is not clear, but the occurrence of deep vein thrombosis or respiratory symptomatology should suggest its presence.

Hyperglycemia

Severe hyperglycemia, sometimes leading to ketoacidosis, has been reported during clozapine treatment in patients with no prior history of hyperglycemia. While a causal relationship to clozapine use has not been definitively established, glucose levels normalized in most patients after discontinuation of clozapine, and a rechallenge in one patient produced a recurrence of hyperglycemia. The effect of clozapine on glucose metabolism in patients with pre-existing diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving clozapine who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycemia, the discontinuation of clozapine should be considered.

Hepatitis

Caution is advised in patients using clozapine who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and pre-existing liver function abnormalities. In patients who develop nausea, vomiting, and/or anorexia during clozapine treatment, liver function tests should be performed immediately. If the elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with clozapine should be discontinued.

0193-06 CLOZAPINE TABLETS

Anticholinergic Toxicity
Clozapine has very potent anticholinergic effects and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. In addition, clozapine use has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction and paralytic ileus (see **ADVERSE REACTIONS**). On rare occasions, these cases have been fatal. Constipation should be initially treated by ensuring adequate hydration, and use of ancillary therapy such as bulk laxatives. Consultation with a gastroenterologist is advisable in more serious cases.
Interference with Cognitive and Motor Performance
Because of initial sedation, clozapine may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness.
Use in Patients with Concomitant Illness
Clinical experience with clozapine in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using clozapine in patients with renal or cardiac disease.
Use in Patients Undergoing General Anesthesia
Caution is advised in patients being administered general anesthesia because of the CNS effects of clozapine. Check with the anesthesiologist regarding continuation of clozapine therapy in a patient scheduled for surgery.
Information for Patients
Physicians are advised to discuss the following issues with patients for whom they prescribe clozapine:
- Patients who are to receive clozapine should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required for the first 6 months. If acceptable WBC counts (WBC greater than or equal to 3,000/mm^3 ANC greater than or equal to 1500/mm^3) have been maintained during the first 6 months of continuous therapy, then WBC counts can be monitored every other week in order to monitor for the occurrence of agranulocytosis, and that clozapine tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.
- Patients should be informed of the significant risk of seizure during clozapine treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking clozapine.
- Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.
- Patients should be informed that if they stop taking clozapine for more than 2 days, they should not restart their medication at the same dosage, but should contact their physician for dosing instructions.
- Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol.
- Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should not breast feed an infant if they are taking clozapine.

Drug Interactions
The risks of using clozapine in combination with other drugs have not been systematically evaluated.
The mechanism of clozapine induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, clozapine should not be used with other agents having a well-known potential to suppress bone marrow function.
Given the primary CNS effects of clozapine, caution is advised in using it concomitantly with other CNS-active drugs or alcohol.
Orthostatic hypotension in patients taking clozapine can, in rare cases (approximately 1 case per 3,000 patients), be accompanied by profound collapse and respiratory and/or cardiac arrest. Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.
Because clozapine is highly bound to serum protein, the administration of clozapine to a patient taking another drug which is highly bound to protein (e.g., warfarin, digitoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clozapine by other highly bound drugs.
Cimetidine and erythromycin may both increase plasma levels of clozapine, potentially resulting in adverse effects.
Although concomitant use of clozapine and carbamazepine is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in clozapine plasma levels. Phenytoin may decrease clozapine plasma levels, resulting in a decrease in effectiveness of a previously effective clozapine dose.
In a study of schizophrenic patients who received clozapine under steady state conditions, fluvoxamine or paroxetine was added in 16 and 14 patients, respectively. After 14 days of co-administration, mean trough concentration of clozapine and its metabolites, N-desmethylclozapine and clozapine N-oxide, were elevated with fluvoxamine by about three-fold compared to baseline concentrations. Paroxetine produced only minor changes in the levels of clozapine and its metabolites. However, other published reports describe modest elevations (less than two-fold) of clozapine and metabolite concentrations when clozapine was taken with paroxetine, fluoxetine, and sertraline. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when clozapine is combined with these drugs, particularly with fluvoxamine. A reduced clozapine dose should be considered.
A subset (3%-10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isozyme P450 2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, the tricyclic antidepressants, and clozapine. These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. In addition, certain drugs that are metabolized by this isozyme, including many antidepressants (clozapine, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isozyme, and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction.
Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6 may require lower doses than usually prescribed for either clozapine or the other drug. Therefore, co-administration of clozapine with other drugs that are metabolized by this isozyme, including antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.
Clozapine may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug induced hypotension because of a possible reverse epinephrine effect.
Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses approximately 7 times the typical human dose on a mg/kg basis. Fertility in male and female rats was not adversely affected by clozapine. Clozapine did not produce genotoxic or mutagenic effects when assayed in appropriate bacterial and mammalian tests.
Pregnancy
Teratogenic Effects
Pregnancy Category B
Reproduction studies have been performed in rats and rabbits at doses of approximately 2-4 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.
Nursing Mothers
Animal studies suggest that clozapine may be excreted in breast milk and have an effect on the nursing infant. Therefore, women receiving clozapine should not breast feed.
Pediatric Use
Safety and effectiveness in pediatric patients have not been established.
ADVERSE REACTIONS
Associated with Discontinuation of Treatment
Sixteen percent of 1080 patients who received clozapine in premarketing clinical trials discontinued treatment due to an adverse event, including both those that could be reasonably attributed to clozapine treatment and those that might more appropriately be considered intercurrent illness. The more common events considered to be causes of discontinuation included: CNS, primarily drowsiness/sedation, seizures, dizziness/syncope, cardiovascular, primarily tachycardias, hypotension and ECG changes; gastrointestinal, primarily nausea/vomiting; hematologic, primarily leukopenia/granulocytopenia/agranulocytosis; and fever. None of the events enumerated accounts for more than 1.7% of all discontinuations attributed to adverse clinical events.
Commonly Observed
Adverse events observed in association with the use of clozapine in clinical trials at an incidence of greater than 5% were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor, autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope, and gastrointestinal complaints, including constipation and nausea, and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be problematic especially during sleep, but may be diminished with dose reduction.
Incidence in Clinical Trials
The following table enumerates adverse events that occurred at a frequency of 1% or greater among clozapine patients who participated in clinical trials. These rates are not adjusted for duration of exposure.

Treatment-Emergent Adverse Experience Incidence Among Patients Taking Clozapine in Clinical Trials (N=842)
(Percentage of Patients Reporting)

Body System Adverse Event[a]	Percent
Central Nervous System	
Drowsiness/Sedation	39
Dizziness/Vertigo	19
Headache	7
Tremor	6
Syncope	6
Disturbed sleep/Nightmares	4
Restlessness	4
Hypokinesia/Akinesia	4
Agitation	4
Seizures (convulsions)	3[b]
Rigidity	3
Akathisia	3
Confusion	3
Fatigue	2
Insomnia	2
Hyperkinesia	1
Weakness	1
Lethargy	1
Ataxia	1
Slurred speech	1
Depression	1
Epileptiform movements/Myoclonic jerks	1
Anxiety	1
Cardiovascular	
Tachycardia	26[b]
Hypotension	9
Hypertension	4
Chest pain/Angina	1
ECG change/Cardiac abnormality	1
Gastrointestinal	
Constipation	14
Nausea	5
Abdominal discomfort/Heartburn	4
Nausea/Vomiting	3
Vomiting	3
Diarrhea	2
Liver test abnormality	1
Anorexia	1
Urogenital	
Urinary abnormalities	2
Incontinence	1
Abnormal ejaculation	1
Urinary urgency/frequency	1
Urinary retention	1
Autonomic Nervous System	
Salivation	31
Sweating	6
Dry mouth	6
Visual disturbances	5
Integumentary (Skin)	
Rash	2
Musculoskeletal	
Muscle weakness	1
Pain (back, neck, legs)	1
Muscle spasm	1
Muscle pain, ache	1
Respiratory	
Throat discomfort	1
Dyspnea, shortness of breath	1
Nasal congestion	1
Hemic/Lymphatic	
Leukopenia/Decreased WBC/Neutropenia	3
Agranulocytosis	1[b]
Eosinophilia	1
Miscellaneous	
Fever	5
Weight gain	4
Tongue numb/sore	1

[a] Events reported by at least 1% of clozapine patients are included.
[b] Rate based on population of approximately 1700 exposed during premarket clinical evaluation of clozapine.
Other Events Observed During the Premarketing Evaluation of Clozapine
This section reports additional, less frequent adverse events which occurred among the patients taking clozapine in clinical trials. Various adverse events were reported as part of the total experience in these clinical studies, a causal relationship to clozapine treatment cannot be determined in the absence of appropriate controls in some of the studies. The table above enumerates adverse events that occurred at a frequency of at least 1% of patients treated with clozapine. The list below includes all additional adverse experiences reported as being temporally associated with the use of the drug which occurred at a frequency less than 1%, enumerated by organ system.
Central Nervous System: loss of speech, amentia, tics, poor coordination, delusions/hallucinations, involuntary movement, stuttering, dysarthria, amnesia/memory loss, histrionic movements, libido increase or decrease, paranoia, shakiness, Parkinsonism, and irritability.
Cardiovascular System: edema, palpitations, phlebitis/thrombophlebitis, cyanosis, premature ventricular contraction, bradycardia, and nose bleed.
Gastrointestinal System: abdominal distention, gastroenteritis, rectal bleeding, nervous stomach, abnormal stools, hematemesis, gastric ulcer, bitter taste, and eructation.
Urogenital System: dysmenorrhea, impotence, breast pain/discomfort, and vaginal itch/infection.
Autonomic Nervous System: numbness, polydypsia, hot flashes, dry throat, and mydriasis.
Integumentary (Skin): pruritus, pallor, eczema, erythema, bruise, dermatitis, petechiae, and urticaria.
Musculoskeletal System: twitching and joint pain.
Respiratory System: coughing, pneumonia/pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, and sneezing.
Hemic and Lymphatic System: anemia and leukocytosis.
Miscellaneous: chills/chills with fever, malaise, appetite increase, ear disorder, hypothermia, eyelid disorder, bloodshot eyes, and nystagmus.
Postmarketing Clinical Experience
Postmarketing experience has shown an adverse experience profile similar to that presented above. Voluntary reports of adverse events temporally associated with clozapine not mentioned above that have been received since market introduction and that may have no causal relationship with the drug include the following:
Central Nervous System: delirium, EEG abnormal; exacerbation of psychosis; myoclonus; overdose; paresthesia; possible mild cataplexy; and status epilepticus.
Cardiovascular System: atrial or ventricular fibrillation and pericardial edema.
Gastrointestinal System: acute pancreatitis; dysphagia; fecal impaction; intestinal obstruction/paralytic ileus; and salivary gland swelling.
Hepatobiliary System: cholestasis; hepatitis, jaundice.
Hepatic System: cholestasis.
Urogenital System: acute interstitial nephritis and priapism.
Integumentary (Skin): hypersensitivity reactions: photosensitivity, vasculitis, erythema multiforme, and Stevens-Johnson Syndrome.
Musculoskeletal System: myasthenic syndrome and rhabdomyolysis.
Respiratory System: aspiration and pleural effusion.
Hemic and Lymphatic System: deep vein thrombosis; elevated hemoglobin/hematocrit; ESR increased; pulmonary embolism; sepsis; thrombocytosis; and thrombocytopenia.
Miscellaneous: CPK elevation; hyperglycemia; hypercalcemia; hyponatremia; and weight loss.
DRUG ABUSE AND DEPENDENCE
Physical and psychological dependence have not been reported or observed in patients taking clozapine.
OVERDOSAGE
Human Experience
The most commonly reported signs and symptoms associated with clozapine overdose are: altered states of consciousness, including drowsiness, delirium and coma; tachycardia; hypotension; respiratory depression or failure; hypersalivation. Aspiration pneumonia and cardiac arrhythmias have also been reported. Seizures have occurred in a minority of reported cases. Fatal overdoses have been reported with clozapine, generally at doses above 2500 mg. There have also been reports of patients recovering from overdoses well in excess of 4 g.
Management of Overdose
Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdosage. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. Additional surveillance should be continued for several days because the risk of delayed effects. Avoid epinephrine and derivatives when treating hypotension, and quinidine and procainamide when treating cardiac arrhythmia.
There are no specific antidotes for clozapine. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.
In managing overdosage, the physician should consider the possibility of multiple drug involvement.
Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physicians' Desk Reference®*.
DOSAGE AND ADMINISTRATION
Upon initiation of clozapine therapy, up to a 1 week supply of additional clozapine tablets may be provided to the patient to be held for emergencies (e.g., weather, holidays).
Initial Treatment
It is recommended that treatment with clozapine begin with one-half of a 25 mg tablet (12.5 mg) once or twice daily and then be continued with daily dosage increments of 25-50 mg/day, if well tolerated, to achieve a target dose of 300-450 mg/day by the end of 2 weeks. Subsequent dosage increments should be made no more than once or twice weekly in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.
In the multicenter study that provides primary support for the effectiveness of clozapine in patients resistant to standard antipsychotic drug treatment, patients were titrated during the first 2 weeks up to a maximum dose of 500 mg/day, on a t.i.d. basis, and were then dosed in a total daily dose range of 100-900 mg/day, on a t.i.d. basis thereafter, with clinical response and adverse effects as guides to the correct dosing.
Therapeutic Dose Adjustment
Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-500 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of clozapine in treatment resistant patients, the mean and the median clozapine doses were both approximately 600 mg/day.]
Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.
Dosing should not exceed 900 mg/day.
Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided.
Maintenance Treatment
While the maintenance effectiveness of clozapine in schizophrenia is still under study, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on clozapine, but at the lowest level needed to maintain remission. Because of the significant risk associated with the use of clozapine, patients should be periodically reassessed to determine the need for maintenance treatment.
Discontinuation of Treatment
In the event of planned termination of clozapine therapy, gradual reduction in dose is recommended over a 1-2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.
Reinitiation of Treatment in Patients Previously Discontinued
When restarting patients who have had even a brief interval off clozapine, i.e., 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25 mg tablet (12.5 mg) once or twice daily (see **WARNINGS**). If that dose is well tolerated, it may be feasible to titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment. However, any patient who has previously experienced respiratory or cardiac arrest with initial dosing, but was then able to be successfully titrated to a therapeutic dose, should be re-titrated with extreme caution after even 24 hours of discontinuation.
Certain additional precautions seem prudent when reinitiating treatment. The mechanisms underlying clozapine-induced adverse reactions are unknown. It is conceivable, however, that re-exposure of a patient might enhance the risk of an untoward event's occurrence and increase its severity. Such phenomena, for example, occur when immune-mediated mechanisms are responsible. Consequently, during the reinitiation of treatment, additional caution is advised. Patients discontinued for WBC counts below 2000/mm^3 or an ANC count below 1000/mm^3 *must not* be restarted on clozapine (see **WARNINGS**).
HOW SUPPLIED
Clozapine Tablets are available as pale yellow, round tablets, debossed "4359" on one side and "25" and a bisect on the other, containing 25 mg clozapine packaged in bottles of 100, 500, 1000, 5000 and unit-dose boxes of 100 tablets. Clozapine Tablets are available as pale yellow, round, flat-faced, beveled-edge tablets with a bisect, debossed "4360" on one side and "100" on the other, containing 100 mg clozapine packaged in bottles of 100, 500, 1000, 4000 and unit-dose boxes of 100 tablets.
PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
Drug dispensing should not ordinarily exceed a weekly supply.
If a patient is eligible for WBC testing every other week, then a two week supply of clozapine can be dispensed.
Dispensing should be contingent upon the results of a WBC count.
Store at controlled room temperature 15°-30°C (59°-86°F).

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